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**Treatment of T3–T4a laryngeal cancer by open partial horizontal laryngectomies: prognostic impact of different pT subcategories**

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Giovanni Succo, surgeon who performed the surgical procedures, study conception and design, drafting the article, final approval of the version to be published; Erika Crosetti, surgeon who performed the surgical procedures, study conception and design, final approval of the version to be published; Andy Bertolin, study conception and design, data collection; Cesare Piazza, study conception and design, drafting the article, final approval of the version to be published; Gabriele Molteni, study conception and design, data collection; Stefano Cirillo, radiologist who reviewed and selected the radiographic findings giving the correct indications for the intervention; Massimo Petracchini radiologist who reviewed and selected the radiographic findings giving the correct indications for the intervention; Martina Tascone, data collection; Andrea E. Sprio, data analysis, statistical analysis, drafting the article; Giovanni N. Berta, drafting the article, final approval of the version to be published; Giorgio Peretti, study conception and design, drafting the article, final approval of the version to be published; Livio Presutti, surgeon who performed the surgical procedures, study conception and design, final approval of the version to be published; Giuseppe Rizzotto, surgeon who performed the surgical procedures, study conception and design, final approval of the version to be published.

**ABSTRACT**

*Background:* The aim of this retrospective study was to identify subcategories in cT3-cT4a supraglottic/glottic cancers, describing their different spreading patterns, and local and loco-regional recurrence modes.

*Methods:* Patients (N=489) who underwent open partial horizontal laryngectomies (OPHLs) were retrospectively classified as: subcategory I (anterior pT3 with normal arytenoid mobility), subcategory II (posterior pT3 with impaired/absent mobility), subcategory III (anterior pT4 with normal mobility), and subcategory IV (posterior pT4 with impaired/absent mobility).

*Results:* Five-year overall, disease-specific, disease-free survivals, loco-regional, local control, freedom from laryngectomy, and laryngectomy-free survival were significantly better in anterior tumors (subcategories I and III) when compared to the corresponding posterior ones (subcategories II and IV).

*Conclusions:* Anterior cT3 tumors are manageable by OPHL, and this approach could also be proposed in the treatment of early anterior cT4aN0. Despite promising results, OPHLs should be considered under investigation in posterior cT3 tumors due to clinical and biological behavior similar to cT4a tumors.

## INTRODUCTION

The current surgical treatment guidelines for laryngeal cancer in its intermediate/advanced categories distinguish T3 lesions in those amenable to partial versus total laryngectomy.<sup>1</sup>

On the other hand, total laryngectomy remains the first therapeutic option for the T4a category, leaving non-surgical organ preservation protocols for selected patients refusing surgery. Nevertheless, to complicate matters further, a lack of evidence-based clear-cut consensus still exists on how to differentiate T3-T4a patients amenable to laryngeal conservation surgery from those requiring total laryngectomy. Different factors related to both the tumor and the patient<sup>2, 3</sup> should indeed be considered when making an appropriate selection between patients treatable by the wide spectrum of open partial horizontal laryngectomies (OPHLs)<sup>4</sup> and those requiring organ sacrifice. One possible source of confusion is related to the great heterogeneity of T3-T4a categories including a wide gamut of different lesions ranging from T3 with minimal versus massive paraglottic space involvement (with normal or impaired/fixed vocal cord and arytenoid mobility), T3 with preepiglottic space infiltration, T3 with thyroid cartilage erosion, T4 with purely anterior extralaryngeal extension, and T4 with posterior-inferior spreading through the lateral portion of the cricothyroid membrane and the crico-thyro-arytenoid space. The contemporary endoscopic<sup>5, 6</sup> and imaging<sup>2, 7</sup> work-ups have dramatically reduced the diagnostic uncertainty level in the pre-treatment setting. Notwithstanding this, no endoscopic technique or imaging refinement is as yet able to objectively quantify the degree and causes of reduced/absent motility of the vocal cord/crico-arytenoid unit.<sup>8</sup>

Nowadays, several surgical and non-surgical options are available for treatment of T3-T4a laryngeal cancer, with comparable results in terms of loco-regional control, overall, and laryngectomy-free survival.<sup>9-11</sup> Some large series published by different authors<sup>12-16</sup> have shown that OPHLs<sup>4</sup> allow sound and reproducible oncological outcomes to be obtained. Furthermore, these techniques are characterized by a high laryngectomy-free survival,

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relatively low morbidity and mortality rates, and acceptable functional outcomes, if a careful preoperative patient selection is carried out.

The aim of this multi-institutional retrospective study on T3-T4a laryngeal cancer patients treated by OPHLs was to identify, in the vast group of these lesions, some homogeneous subcategories describing their different patterns of spreading and related modes of local, and loco-regional recurrence.

For Peer Review

## PATIENTS AND METHODS

### *Patients*

After comprehensive preoperative counseling, 479 patients (Table 1) underwent surgery between January 2000 and December 2012 at the Hospitals of Vittorio Veneto, Martini of Turin, and Policlinic Hospital of Modena. As previously described,<sup>15</sup> patient selection was based on superficial and deep tumor extent, assessed by endoscopic and imaging evaluation performed less than 3 weeks before surgery. Computed tomography (CT) or magnetic resonance (MR) imaging was used to define infiltration of the cartilaginous framework, involvement of the pre-epiglottic (PES) and/or paraglottic spaces (PGS), as well as extralaryngeal spreading. Pre- and intraoperative videolaryngoscopic examination, by flexible endoscope in the office, and 0° and 70° rigid endoscopes in the operating theater, were employed to evaluate both vocal cord/arytenoid mobility and superficial tumor extent. Concerning arytenoid mobility, 293 patients showed impaired mobility/fixed vocal cord with mobile arytenoid, and 186 presented both vocal cord and arytenoid fixation. Patient characteristics, distribution according to the involved laryngeal sites, as well as their pT and pN categories, are reported in Table 1.

The general eligibility criteria for OPHL were a histological diagnosis of intermediate/advanced (cT3-cT4a) categories of glottic and supraglottic laryngeal squamous cell carcinoma (SCC), and Karnofsky index<sup>17</sup> higher than 80. Exclusion criteria were: purely supraglottic T3 with limited extension to the PES (and therefore amenable to OPHL type I or transoral laser microsurgery), previous treatment(s) for laryngeal carcinoma with curative intent, severe diabetes mellitus, severe bronchopulmonary chronic obstructive disease, neurological problems impairing the ability to expectorate and/or swallow, or severe cardiac disease.

### *pT subcategories*

Clinical, endoscopic, radiologic, surgical, and pathological reports were retrospectively assessed to divide patients into four subcategories based on a laryngeal compartmentalization using a vertical virtual plane tangential to the arytenoid vocal process and perpendicular to the ipsilateral thyroid lamina. We defined anterior and posterior laryngeal compartments as the portions located, respectively, anteriorly or posteriorly to such a plane (Fig. 1). The four subcategories identified are therefore as follows:

I) Supraglottic/glottic/subglottic pT3, involving the anterior laryngeal compartment, with PES and anterior PGS involvement with/without inner cortex thyroid infiltration, but with normal arytenoid mobility (n=233 patients) (Fig. 2);

II) Supraglottic/glottic/subglottic pT3, involving the posterior laryngeal compartment, with infiltration of the whole PGS with/without inner cortex thyroid invasion, and with impaired (reduced or absent) arytenoid mobility (n=157 patients) (Fig. 3);

III) Supraglottic/glottic/subglottic pT4a, involving the anterior laryngeal compartment, with extralaryngeal extension (through the thyro-hyoid membrane, thyroid cartilage, and/or crico-thyroid membrane), but with normal arytenoid mobility (n=60 patients) (Fig. 4);

IV) Supraglottic/glottic/subglottic pT4a, involving the posterior laryngeal compartment, with extralaryngeal extension (through or around the posterior portion of the thyroid lamina, through the lateral crico-thyroid membrane, cricoid cartilage, and/or at the level of the crico-thyroid-arytenoid space), and with impaired (reduced or absent) arytenoid mobility (n=29 patients) (Fig. 5).

### *Surgical procedures*

All 479 patients underwent OPHL types II-III according to the European Laryngological Society Classification<sup>8</sup> for curative purposes. Indications and contraindications of such



procedures have already been described in previous studies.<sup>12, 14, 15, 18, 19</sup> The different types of surgical operation performed are reported in Table 2.

Neck dissection (ND), graded according to the American Academy of Otolaryngology – Head and Neck Surgery Foundation Classification,<sup>20</sup> was performed in 419 patients (87.5%), and was unilateral in 347 (82.8%) and bilateral in 72 (17.2%). ND was performed electively (ND levels II-IV) in 368 cN0 patients (87.8%) and for curative purposes in 51 cN>0 (12.2%). In 391 patients (93.3%), level VI or unilateral paratracheal lymph node clearance was added. No ND was performed in 60 cN0 patients (12.5%).

### *Adjuvant treatments*

Based on pathological findings, 62 patients (12.9%) were subjected to adjuvant radiotherapy. The indications were: pN+>1 (n=43 patients), gross extralaryngeal extension (n=17, of whom six showed positive margins), and positive margins elsewhere (n=2). A large volume encompassing the primary site and all draining lymph nodes were irradiated with a dose of up to 54 Gy. Regions at higher risk for malignant dissemination received a 12 Gy boost (total, 66 Gy; range, 62–68 Gy).

Furthermore, chemotherapy was added in 37 patients who received 100 mg/m<sup>2</sup> of cisplatin on days 1, 22, and 43, concomitantly with radiotherapy because of a higher risk of local recurrence (five with Delphian nodes pN+, 20 pN2 with extracapsular spread, and 12 more extended pT4a showing positive/close margins toward pre-laryngeal tissues).<sup>21</sup>

### *Statistical methods*

Clinical, endoscopic, and radiologic follow-up was performed for a mean of 5.3 years (range, 6 months–16.4 years). Overall (OS), disease-free (DFS), disease-specific (DSS) survivals, local (LC) and loco-regional (LRC) controls with OPHL alone, laryngectomy-free (LFS), and laryngo-esophageal dysfunction-free survivals (LEDFS)<sup>22</sup> were assessed by

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Kaplan–Meier curves. Log-rank (LR) and, for early events, Gehan-Breslow-Wilcoxon (GBW) tests were used to compare Kaplan–Meier estimates among the different subcategories. The end points considered were: the date of death (OS); the date of the first recurrence (DFS); the date of death from disease (DSS); the date of the first local recurrence (LC); the date of the first loco-regional recurrence (LRC); the date of salvage total laryngectomy or the date of death (LFS); the date of salvage total laryngectomy or the date of tracheostomy and/or PEG for functional reasons or the date of death (LEDFS). The association of prognostic factors for recurrence and subcategories was evaluated by odds ratio, meanwhile the corresponding incidences were compared by chi-squared ( $\chi^2$ ) test. All analyses were performed with GraphPad Prism version 6.0e (GraphPad Software, San Diego, CA, USA), with  $p<0.05$  as the threshold for statistical significance.

## RESULTS

### *Pathology*

Pathology reports showed close margins ( $<2$  mm on the specimen side) in 59 cases (12.3%) and positive margins (negative at frozen sections but positive at the definitive histopathologic examination) in 16 (3.3%).

Comparison between clinical and pathological staging showed up-staging of the primary tumor in 73 (15.2%) cT3 lesions that became pT4a (49 in subcategory III and 24 in subcategory IV), while 6 cT4a tumors became pT3 (3 in subcategory I and 3 in subcategory II).

In total, 428 patients (89.3%) had been staged as cN0. In contrast, 40 (9.3%) of them became pN+ after ND. Overall, lymph node metastases were detected in 72 (15%) patients of whom 41 (8.6%) had multiple metastases (Table 1).

### *Patterns of failure*

In total, 70 (14.6%) patients developed recurrences: 28 (40%) were local, 18 (25.7%) regional, and 4 (5.7%) loco-regional. Seven (10%) had local and distant recurrences, 2 (2.8%) were regional and distant, whereas 10 (14.3%) developed distant metastasis only. One patient (1.4%) developed both loco-regional and distant recurrences.

### *Survival and disease control according to different subcategories*

The 5-year estimates of the abovementioned oncologic outcomes for each subcategory are reported in Table 3. OS was significantly higher ( $p<0.01$ , with LR and GBW tests) in patients affected by anterior tumors (subcategories I and III, 92.7%) when compared with those treated for posterior ones (subcategories II and IV, 82.3%) (Fig. 6A). Moreover, anterior pT3 tumors (subcategory I) had better OS than posterior pT3 tumors (subcategory II,  $p<0.001$ , with LR and GBW tests), although no significant difference was detected

among pT4 tumors (subcategories III vs. IV). Finally, OS was hampered by T classification in anterior tumors (subcategories I vs. III,  $p<0.01$ , with LR and GBW tests), but not in posterior ones (subcategories II vs. IV).

In the same way, DSS was affected by the described laryngeal compartmentalization: it was 96.3% in anterior (subcategories I and III) and 90.1% in posterior tumors (subcategories II and IV) ( $p<0.05$ , with LR and GBW tests) (Fig. 6B). A statistically significant difference was also demonstrated when comparing anterior (subcategory I) and posterior (subcategory II) pT3 tumors ( $p<0.05$ , with LR and GBW tests), but not when analyzing pT4 tumors (subcategories III vs. IV), even though they had a similar trend. Finally, no difference in terms of DSS was detected by comparison of pT3 and pT4 tumors located in the same laryngeal compartment (subcategories I vs. III and II vs. IV).

DFS was significantly reduced in posterior (subcategories II and IV, 78.8%) compared to anterior tumors (subcategories I and III, 88.3%) ( $p<0.05$ , with LR and GBW tests) (Fig. 6C). Likewise, posterior pT3 (subcategory II) had worse DFS ( $p<0.05$ , with LR and GBW tests) than anterior pT3 tumors (subcategory I), although no significant difference was detected among subcategories III and IV. Moreover, patients treated for pT4 tumors had more recurrences than those with pT3 neoplasms independently from the antero-posterior localization of the disease (subcategories I vs. III,  $p<0.01$ ; subcategories II vs. IV,  $p<0.05$ , with LR and GBW tests).

LRC was not significantly different between anterior (subcategories I and III, 88.6%) and posterior tumors (subcategories II and IV, 83.3%) (Fig. 6D). Nevertheless, it was better in subcategory I than in subcategory II ( $p<0.05$ , with LR test), although pT4 (subcategories III and IV) had comparable results. Finally, T status affected LRC of anterior tumors (subcategories I vs. III,  $p<0.01$ , with LR and GBW tests), but not that of posterior ones (subcategories II vs. IV).

Likewise, LC was similar in anterior (subcategories I and III, 92.7%) and posterior tumors (subcategories II and IV, 88.1%) (Fig. 6E). Again, subcategory I had better control than subcategory II ( $p < 0.05$ , with LR test), whereas no significant difference was detected when comparing pT4 (subcategories III vs. IV).

Patients affected by anterior tumors were less prone to fatal outcomes and had less need of salvage total laryngectomy than those with posterior ones (LFS 90.1% for subcategories I and III and 75.7% for subcategories II and IV;  $p < 0.001$  with LR test and  $p < 0.01$  with GBW test) (Fig. 6F). Subcategory I had better LFS than subcategory II ( $p < 0.001$ , with LR and GBW tests), but no significant difference was detected between subcategories III and IV. Finally, LFS was higher in anterior pT3 than in anterior pT4 tumors ( $p < 0.01$ , with LR and GBW tests), whereas posterior pT3 had better LFS with respect to posterior pT4 tumors as an early event only ( $p < 0.05$ , with GBW test).

Similarly, the LEDFS was higher in anterior (subcategories I and III, 88.8%) than in posterior tumors (subcategories II and IV, 74.9%,  $p < 0.001$ , with LR test and  $p < 0.01$ , with GBW test) (Fig. 6G). Again, despite no significant difference being detected between pT4 tumors (subcategories III vs. IV), anterior pT3 (subcategory I) had better LEDFS than posterior pT3 tumors (subcategory II,  $p < 0.001$ , with LR and GBW tests). Furthermore, only anterior tumors were affected by T classification: anterior pT4 (subcategory III) had worse LEDFS ( $p < 0.001$ , with LR and GBW tests) than anterior pT3 (subcategory I).

#### *Correlation between each subcategory and factors affecting loco-regional recurrence*

The associations between positive or close margins, pN+, level VI pN+, extracapsular spread (ECS) and subcategories have been evaluated and results are summarized in Table 4.

Tumor localization was generally associated with the occurrence of ECS alone: its risk of occurrence was indeed higher in posterior (subcategories II and IV) than in anterior tumors

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(subcategories I and III) ( $p<0.05$ ). Despite being not significantly different, the occurrence of ECS appeared to be more frequent in subcategory IV.

The prevalence of positive margins was homogeneous amongst the subcategories, but their occurrence was significantly more frequent in pT4a when compared with pT3 tumors (subcategory III vs. I,  $p<0.05$ ; subcategory IV vs. II,  $p<0.001$ ). Similarly, no statistically significant difference was detected in terms of pN+ prevalence amongst the subcategories, but lymph node involvement at level VI was more common in patients affected by pT4a tumors, with respect to those with pT3 tumors (subcategory III vs. I,  $p<0.001$ ; subcategory IV vs. II,  $p<0.01$ ).

## DISCUSSION

The last two decades have gradually witnessed a paradigm shift in the treatment of laryngeal cancer, with a progressively increasing significance given to organ and function preservation.<sup>9-11, 15, 16</sup> Focusing on advanced stages, all the therapeutic approaches, non-surgical as well as surgical by OPHLs, have demonstrated that larynx preservation is feasible, even though some disappointing long-term results of chemoradiotherapy (CRT) protocols deserve further evaluation and investigation.<sup>9, 23</sup>

Despite the undoubted advantages deriving from the laryngeal function preservation approach in terms of quality of life, laryngeal oncology has struggled to develop like other subspecialties in oncology, probably because of the major push towards organ preservation by non-surgical modalities. In fact, this paper clearly demonstrates that excellent results can be obtained even though the application of surgical function sparing strategies like OPHLs maintained that particular accuracy in their indications and limits are observed. From this perspective, the implementation of correct OPHL indications, rather than the surgical technique itself, is probably one of the most important keys to success in this type of surgery.

Assuming that total laryngectomy is the safest treatment for laryngeal cancer in intermediate and advanced stages, any therapeutic approach attempting to preserve the larynx should be based on careful case selection, where a pivotal role is taken by patient- and tumor-related parameters. For this reason, meaningful direct comparisons between the oncologic and functional outcomes of CRT, total laryngectomy and OPHLs are lacking in the current literature for the very reason that they are quite difficult, if not impossible, to be comprehensively made. For the innate diversity (in terms of staging, comorbidity, willingness, age, gender, profession, previous treatments, etc.) of those patients considered amenable to one treatment versus another, a true comparison of crude data

like survival or swallowing/voice (just to mention the most obvious) is far beyond the real possibilities of any prospective or retrospective analysis.

OPHL can be offered to patients as a valuable alternative to preserve part of the larynx and its functions, even in advanced T categories, avoiding the negative physical and psychosocial impacts of a permanent tracheostomy<sup>15, 16, 19</sup>. After a strict selection of patients (based on the assessment of good general and functional conditions, the absence of clinically positive neck nodes and a good compliance to an intensive rehabilitation protocol), different types of partial laryngectomy can be proposed. When a patient accepts a conservative surgical management approach, in fact, an OPHL type I, IIa, IIb, IIIa or IIIb may be performed guided by intraoperative evaluations confirmed by frozen sections. This kind of flexibility and customized surgical approach requires specific expertise and, therefore, centralization of such cases in sufficiently large reference centers.

Further aspects to be considered during pre-treatment multidisciplinary visit are the well-known absolute contraindications to OPHL type II and III, which are based on T and N stage.

In our experience, these are represented by: i) lesions extended to base of tongue or pyriform sinus; ii) lesions with major invasion of pre-epiglottic space involving the hyoid bone, lesion involving the inter-arytenoid space, the posterior commissure and both arytenoid cartilages; iii) large extralaryngeal spread of cancer involving thyroid gland, strap muscles, cervical skin, internal jugular vein or common carotid artery; and iv) lesions reaching the first tracheal ring.

The suspected presence of clinically positive nodes >cN1 is not an absolute contraindication. However, it does not represent a good indication to OPHL due to the probable need for a post-operative RT: the first goal of a function sparing surgical approach should indeed be to get a single-shot therapy.



In the present series, stringent clinical-radiological selection criteria have been adopted to identify homogeneous cT3 and cT4 subcategories that may be treated by OPHL type II – III with the best chance of success. For both supraglottic and glottic T3 and T4 tumors, the most crucial prognosticator appears to be involvement of the posterior PGS, usually associated with reduced mobility or fixation of the ipsilateral arytenoid. This simple criterion of anterior vs. posterior laryngeal compartmentalization has herein been demonstrated to be a useful adjunctive parameter to be included in preoperative therapeutic planning.

In fact, when dealing with anterior T3 tumors with normal vocal cord/arytenoid mobility (subcategory I), OPHL compares favorably with transoral laser microsurgery (TLM) (whose local control has been shown to be in the range of 44–72% for glottic and 70–87% for supraglottic tumors),<sup>24–27</sup> and with CRT (whose 2-year laryngo-esophageal dysfunction-free survival has been reported to be around 40%).<sup>28</sup> The inner thyroid lamina infiltration does not negatively impact on the possibility to attain adequate disease control by such an open-neck conservative approach, while this is definitely the case for TLM and the issue is still debated for CRT.

Considering anterior T4 tumors (subcategory III), OPHL allows quite favorable oncologic outcomes that can only be compared with those described after total laryngectomy. Here the difference is in terms of a better quality of life and function preservation of the larynx. Interestingly, our series highlights that there is not a great difference in terms of OS, DSS, and LFS between subcategory I and III when these lesions have been addressed by OPHL.

In contrast, the posterior lesions are much more troublesome and definitely represent the most difficult clinical scenario. Posterior T3 tumors with vocal cord/arytenoid fixation (subcategory II) have been shown to offer very poor outcomes when treated by either TLM or CRT. Even using OPHLs, the oncologic outcomes are significantly worse in this

subcategory when compared to anterior tumors (OS  $p<0.001$ , DSS  $p<0.05$ , and DFS  $p<0.001$ ).

OPHLs for T3 cancer affecting arytenoid motility requires a detailed knowledge of tumor growth and diffusion patterns. Traditionally, arytenoid fixation was adopted as an exclusion criterion for OPHLs. However, in a study on 77 cases, Katilmis et al. focused on the possible different causes of arytenoid fixation: involvement of intrinsic laryngeal muscles with insertion on the arytenoid, crico-arytenoid joint invasion, and recurrent nerve infiltration.<sup>29</sup> Beyond these, another cause of reduced/absent arytenoid mobility is represented by the tumor mass effect, which is present in about 60% of supraglottic lesions. Therefore, an adequate preoperative endoscopic and imaging work-up able to reliably distinguish among such different causes of arytenoid fixation is strongly warranted and might in future greatly help in subclassifying these lesions according to more detailed etiologies. This may also mean that posterior T3 tumors could be considered more similar to T4 from an oncologic as well as from a functional point of view. Even from an anatomic perspective, posterior T3 tumors can present cricoarytenoid joint invasion, cricoid plate infiltration, as well as lateral cricoarytenoid muscle involvement, or perineural spreading along the recurrent nerve. These factors allow tumors to grow outside the laryngeal box, towards the hypopharynx and cervical soft tissues. Once the tumor has gained the thyro-cricoarytenoid gateway, it is indeed almost outside the larynx and, in this sense, it is prognostically more similar to T4 cancer. Moreover, in posterior T3-T4 tumors, the risk of occurrence of lymph nodes with ECS is 2.5 times higher than in anterior lesions, and the occurrence of close margins is 2.4 times higher in anterior pT4 than in pT3, and 8.1 times higher in posterior lesions. In light of this, OPHL should be reserved for very carefully selected cases of posterior T3 (and even less frequently in posterior T4 or subcategory IV) since, even from a functional point of view, OPHL type III + CAU (removal of one cricoarytenoid unit) definitively represents an “extreme” conservative surgery with several

technical difficulties and sometimes unpredictable outcomes. Therefore, in posterior T3-T4 tumors, total laryngectomy (with adjuvant CRT or RT) should remain the mainstay of treatment.

Another advantage of OPHLs type II – III is their respectable functional outcomes whose occurrences have been summarized in Table 5. As a matter of fact, use of OPHL allows quite good results to be obtained in terms of the composite end point represented by LEDFS. Even from this point of view, anterior pT3 (subcategory I) had better LEDFS than posterior pT3 tumors (subcategory II,  $p < 0.001$ , with LR and GBW tests).

Recently, comparing CRT versus primary surgery, Timme et al. showed that some selected patients with locally advanced laryngeal cancer can be offered non-surgical organ preservation without compromising survival.<sup>28</sup> However, these have higher rates of laryngeal and esophageal dysfunction than those obtained by OPHLs.

## CONCLUSIONS

OPHLs type II – III for intermediate/locally advanced laryngeal cancer provide good oncological and functional outcomes only if strict patient and tumor selection criteria are followed. Concerning the cT3 category, anterior tumors sparing the posterior PGS and not affecting arytenoid mobility are definitely manageable by such a surgical approach with excellent oncologic outcomes. OPHLs could also be offered to patients affected by early anterior cT4aN0, strongly motivated to avoid total laryngectomy and declining concurrent CRT.

Even though associated with more than promising results, probably due to the strict criteria used to select the subset of patients more suitable for partial laryngectomies, this conservative surgical approach should be carefully applied in cases of cT3 tumors reaching the posterior PGS and causing arytenoid fixation. In fact, the subset of patients

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belonging to subcategory II comprises tumors characterized by biological behavior as well as oncologic results that appear very similar to those of T4a cancers.

Anyway, a new method of selecting cases amenable to OPHL should first keep in mind the absolute local and general contraindications to this type of surgery.

For Peer Review

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## FIGURE LEGENDS

**Fig. 1** – Anatomical drawings representing the anterior and posterior laryngeal compartments defined by a vertical plane tangential to the arytenoid vocal process and perpendicular to the ipsilateral thyroid lamina: A) axial; B) sagittal views.

**Fig. 2** – Anatomical drawings representing the possible tumor presentations in subcategory I. A) Supraglottic cT3 extending to the PES and anterior commissure; B) supraglottic cT3 with PES and anterior PGS involvement; C) glotto-supraglottic cT3 with anterior PGS and infrapetiole region involvement; D) glottic cT3 with anterior PGS involvement; E) glottic cT3 with anterior PGS, internal thyroid lamina, and anterior commissure involvement; F) glottic-subglottic cT3 with anterior PGS and subglottic mucosa involvement.

**Fig. 3** – Anatomical drawings representing the possible tumor presentations in subcategory II. A) Supraglottic cT3 with superior and posterior PGS and arytenoid involvement; B) glottic cT3 with whole PGS involvement; C) glottic cT3 with whole PGS and internal thyroid lamina involvement; D) glotto-subglottic cT3 with posterior PGS and crico-arytenoid joint involvement.

**Fig. 4** – Anatomical drawings representing the possible tumor presentations in subcategory III. A) Anterior supraglottic cT4a with extension through the thyro-hyoid membrane and thyroid cartilage; B) anterior glottic cT4a with extension through the thyroid cartilage and crico-thyroid membrane.

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**Fig. 5** – Anatomical drawings representing the possible tumor presentations in subcategory IV. A) Posterior glottic cT4a with extension through the crico-thyroid membrane; B) posterior transglottic cT4a with extension through the thyroid cartilage and cricoid involvement.

**Fig. 6** – A) Overall survival, B) disease-specific survival, C) disease-free survival, D) locoregional control, E) local control, F) laryngectomy-free survival, and G) laryngo-esophageal dysfunction-free survival for the entire cohort. Log-Rank test: \* $p<0.05$ ; \*\* $p<0.01$ ; \*\*\* $p<0.001$ . Gehan-Breslow-Wilcoxon test: # $p<0.05$ ; ## $p<0.01$ .



Table 1 – Epidemiologic and clinical characteristics of patients treated by OPHL in the present series (N=479).

		No of patients (%)
<b>Age</b>	Mean ± standard deviation	60.0±9.2
	Range	16-83
<b>Gender</b>	Male	434 (90.6%)
	Female	45 ( 9.4%)
<b>Karnofsky</b>	100	298 (62.2%)
	90	181 (37.8%)
<b>Arytenoid mobility</b>	Normal	293 (61.2%)
	Impaired/fixed	186 (38.8%)
<b>pTN</b>		
pT3	N0	290 (60.5%)
	N1	15 ( 3.1%)
	N2	18 ( 3.8%)
pT4a	N0	69 (14.4%)
	N1	8 ( 1.7%)
	N2	7 ( 1.5%)
<b>Total</b>		407 (85.0%)
		72 (15.0%)

Table 2 – Surgical procedures performed in the 479 patients included in this study

OPHL type	Subcategory I	Subcategory II	Subcategory III	Subcategory IV
Ila, n (%)	33/233 (14.2%)	15/157 ( 9.6%)	7/60 (11.7%)	4/29 (13.8%)
Ila + ARY, n (%)	125/233 (53.6%)	69/157 (43.9%)	11/60 (18.3%)	6/29 (20.7%)
IIb, n (%)	19/233 ( 8.2%)	6/157 ( 3.8%)	6/60 (10.0%)	0/29 ( 0.0%)
IIb + ARY, n (%)	49/233 (21.0%)	37/157 (23.6%)	19/60 (31.7%)	5/29 (17.3%)
IIIa, n (%)	1/233 ( 0.4%)	2/157 ( 1.3%)	3/60 ( 5.0%)	1/29 ( 3.4%)
IIIa + CAU, n (%)	6/233 ( 2.6%)	28/157 (17.8%)	10/60 (16.7%)	10/29 (34.5%)
IIIb, n (%)	0/233 ( 0.0%)	0/157 ( 0.0%)	2/60 ( 3.3%)	1/29 ( 3.4%)
IIIb + CAU, n (%)	0/233 ( 0.0%)	0/157 ( 0.0%)	2/60 ( 3.3%)	2/29 ( 6.9%)

Ila: supracricoid partial laryngectomy with crico-hyoido-epiglottopexy; IIb: supracricoid partial laryngectomy with crico-hyoidopexy; IIIa: supratracheal partial laryngectomy with tracheo-hyoido-epiglottopexy; IIIb: supratracheal partial laryngectomy with tracheo-hyoidopexy; ARY: removal of one arytenoid; CAU: removal of one cricoarytenoid unit.

Table 3 – Kaplan-Meier estimates of 5-year oncologic outcomes stratified according to subcategory

	Subcategory			
	I	II	III	IV
OS, %	95.0	82.8	82.9	79.9
DSS, %	97.0	90.7	93.6	86.5
DFS, %	91.5	81.2	74.6	64.2
LRC, %	91.9	84.2	74.6	77.3
LC, %	96.0	89.1	78.1	81.6
LFS, %	93.0	77.7	77.2	64.1
LEDFS, %	93.1	76.6	70.4	64.7

OS = overall survival; DSS = disease-specific survival; DFS = disease-free survival; LRC = locoregional control; LC = local control; LFS = laryngectomy-free survival; LEDFS = laryngo-esophageal dysfunction-free survival.

Table 4 – Prognostic factors for recurrences. ODDS Ratio and  $\chi^2$  analyses amongst subcategories.

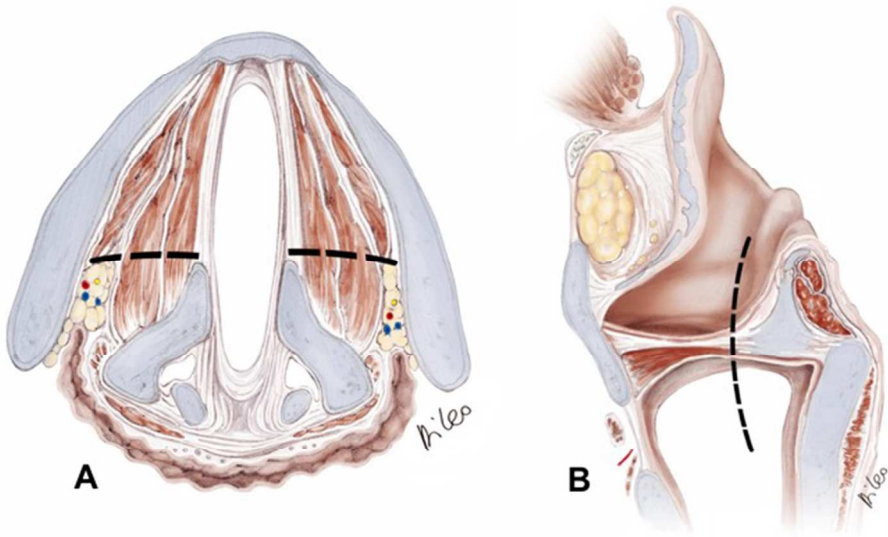
	Subcategory				
	II vs. I	IV vs. III	III vs. I	IV vs. II	II+IV vs. I+III
<b>ODDS Ratio</b>					
Close margins	0.65	2.20	2.41	8.13	0.93
Positive margins	2.70	1.40	3.12	1.61	2.08
pN+	1.69	2.13	1.74	2.20	1.32
Level VI+	3.77	2.32	11.69	7.20	2.14
ECS	2.03	7.51	1.09	4.05	2.53
<b><math>\chi^2</math></b>					
Close margins	0.349	0.172	0.032	0.000	0.907
Positive margins	0.196	0.899	0.312	0.927	0.233
pN+	0.514	0.470	0.330	0.179	0.353
Level VI+	0.106	0.418	0.000	0.006	0.118
ECS	0.292	0.062	0.766	0.076	0.047

ECS, extracapsular spread.

Table 5 – Occurrence of functional impairments after OPHLs stratified according to subcategory

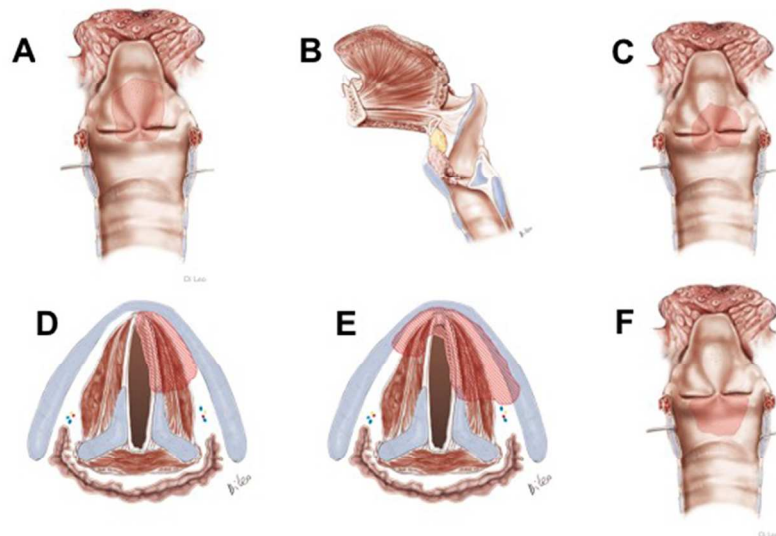
	Subcategory			
	I	II	III	IV
Permanent nasogastric tube	1/233 (0.4%)	0/157 (0.0%)	0/60 (0.0%)	3/29 (10.3%)
Permanent percutaneous endoscopic gastrostomy	4/233 (1.7%)	0/157 (0.0%)	0/60 (0.0%)	1/29 ( 3.4%)
Permanent tracheostomy	3/233 (1.3%)	8/157 (5.1%)	4/60 (6.7%)	2/29 ( 6.9%)
Severe vocal communication impairment	2/233 (0.8%)	6/157 (3.8%)	2/60 (3.3%)	1/29 ( 3.4%)

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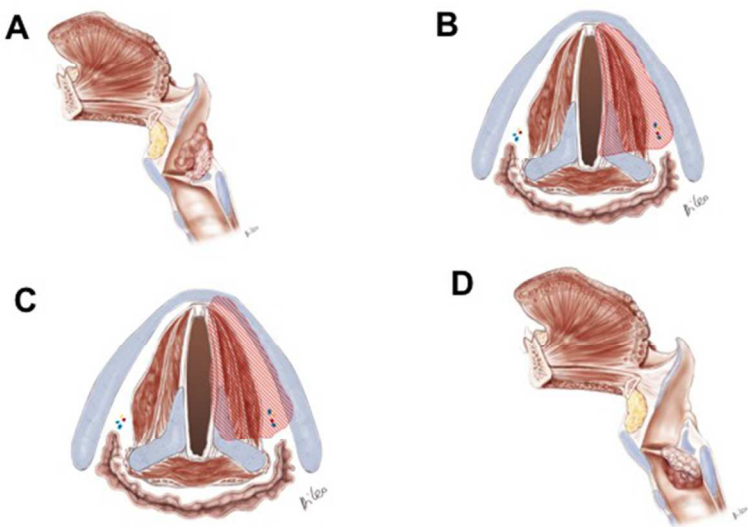
Anatomical drawings representing the anterior and posterior laryngeal compartments defined by a vertical plane tangential to the arytenoid vocal process and perpendicular to the ipsilateral thyroid lamina: A) axial; B) sagittal views.

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Anatomical drawings representing the possible tumor presentations in subcategory I. A) Supraglottic cT3 extending to the PES and anterior commissure; B) supraglottic cT3 with PES and anterior PGS involvement; C) glotto-supraglottic cT3 with anterior PGS and infrapetiole region involvement; D) glottic cT3 with anterior PGS involvement; E) glottic cT3 with anterior PGS, internal thyroid lamina, and anterior commissure involvement; F) glottic-subglottic cT3 with anterior PGS and subglottic mucosa involvement.

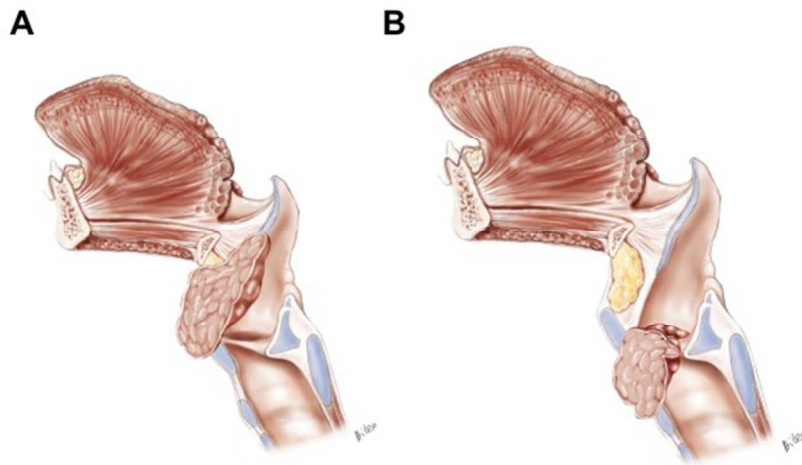
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Anatomical drawings representing the possible tumor presentations in subcategory II. A) Supraglottic cT3 with superior and posterior PGS and arytenoid involvement; B) glottic cT3 with whole PGS involvement; C) glottic cT3 with whole PGS and internal thyroid lamina involvement; D) glotto-subglottic cT3 with posterior PGS and crico-arytenoid joint involvement.

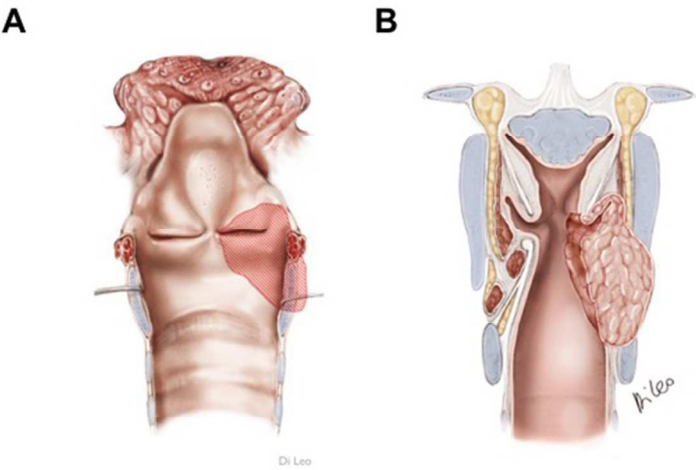
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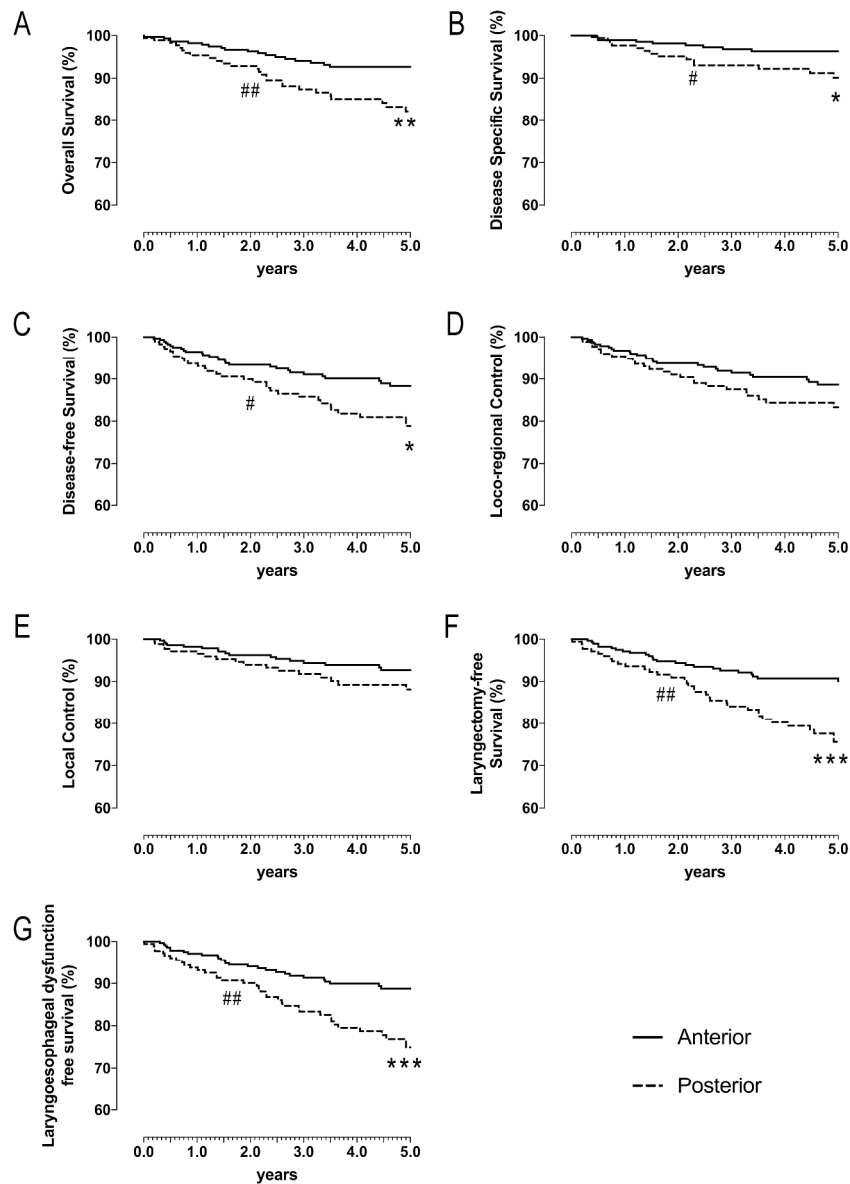
Anatomical drawings representing the possible tumor presentations in subcategory III. A) Anterior supraglottic cT4a with extension through the thyro-hyoid membrane and thyroid cartilage; B) anterior glottic cT4a with extension through the thyroid cartilage and crico-thyroid membrane.

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Anatomical drawings representing the possible tumor presentations in subcategory IV. A) Posterior glottic cT4a with extension through the crico-thyroid membrane; B) posterior transglottic cT4a with extension through the thyroid cartilage and cricoid involvement.

140x78mm (300 x 300 DPI)



A) Overall survival, B) disease-specific survival, C) disease-free survival, D) locoregional control, E) local control, F) laryngectomy-free survival, and G) laryngo-esophageal dysfunction-free survival for the entire cohort. Log-Rank test: \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ . Gehan-Breslow-Wilcoxon test: # $p < 0.05$ ; ## $p < 0.01$ .

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